PERTUSSIS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY TRAVENOL LABORATORIES, INC. HYLAND DIVISION

1. Description. This product is a 16.5 (± 1.5) percent solution of the immunoglobulin fraction (Cohn Fraction II) of the serum of healthy adults hyperimmunized with pertussis vaccine. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. Cryoprecipitate is removed by centrifugation and reserved for other use. Fraction II is obtained from Fraction I, II, III by the Cohn method with some modifications. Donors are given 3 doses (0.5 ml) of pertussis vaccine subcutaneously at weekly intervals, the fourth dose is given after 4 weeks, and later doses are given at 4 week intervals as long as the donor remains on the program. Plasmapheresis is performed twice weekly.

The product is available in 1.5 ml single dose vials.

2. Labeling--a. Recommended use/indiciations. In prophylaxis, one 1.5 ml dose of pertussis immune globulin (human) is recommended for a child as soon after exposure as possible. A second dose, 1 week after the first, is desirable. If use of the globulin is delayed more than 1 week after exposure, larger doses should be given at 1 to 2 week intervals.

In treatment, for children already showing symptoms of pertussis, one 1.5 ml dose should be given as soon as possible, with additional doses at 2 day intervals until recovery has begun. For critically ill

children, the initial dose might well be doubled. In cases of pertussis pneumonitis, the globulin treatment may be supplemented with suitable sulfonamide or antibiotic therapy.

It is clearly stated that the product should be given intramuscularly and not intravenously.

b. Contraindications. None are listed. Under reactions the remote possibility of serum sickness and anaphylaxis are mentioned, as well as local tenderness and stiffness. A warning against intravenous injection is given.

3. Analysis--a. Efficacy--(1) Animal. Not applicable.

(2) Human. The manufacturer's submission to the Panel (Ref. 4) cites the literature of pertussis immune globulin, but they appear not to have conducted any field tests of their own product. The product is tested for potency by measurement of agglutination titers. The agglutination titers of the lot under test, a house reference lot, and the starting plasma pool are determined, using as the antigen a commercially available licensed pertussis vaccine, always from the same manufacturer. The lot under test must show at least 16 times concentration of antibody over the starting plasma pool (i.e., 4 doubling dilutions difference) and the house reference lot must show the same titer as it showed in previous tests, plus or minus 1 doubling dilution. No reference or standard from the Bureau of Biologics is being utilized.

b. Safety. This product is tested for purity, residual moisture, pyrogens, electrophoretic purity, "general safety," and stability.

(1) Animal. This product meets Federal requirements.

(2) Human. No data on human safety for this specific product were supplied other than from the general literature. No data from the manufacturer's complaint file were submitted.

c. Benefit/risk ratio. The benefits of this product both for use in prophylaxis and treatment are questionable. Several uncontrolled studies report beneficial results, but the controlled studies, even those investigating the prophylactic use (Morris (Ref. 5) and Place (Ref.6)) report no significant differences between patients given pertussis immune globulin and other material. The risks are minimal, but allergic reactions and isoimmunization have to be considered.

4. Critique. The most difficult problem is to determine if the current literature supports the belief that the use of pertussis immune globulin is effective in prophylaxis, let alone treatment of pertussis. The manufacturer's own product has not been field tested; however, such a test would be very difficult to institute. Data from complaint files are lacking. The Bureau of Biologics does provide a United States standard antipertussis serum, and the provisional requirements state that each lot of pertussis immune globulin shall contain a pertussis antibody level of not less than 500 pertussis units per vial compared with this standard. Information on adverse reactions to repeated administration of pertussis vaccine in adults, a procedure utilized in the production of pertussis immune globulin (human), should be developed. This information should include data on the type of vaccine used.

Since sulfonamides are not the first choice in treatment of pertussis, the advice regarding supplementary treatment should be reworded: substitute "sulfonamide or antibiotic therapy" with "antimicrobial therapy."

5. Recommendations. The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for period not to exceed 3 years during which time the manufacturer shall develop data regarding the efficacy of this product.

REFERENCES

(1) BER VOLUME 2023.

(2) Hatz, F. and C. Burckhardt, "Human Hyperimmune Serum and Streptomycin as Therapy for Pertussis in Infants and Small Children," Annals of Pediatrics, 175:274-284, 1950.

(3) Krugman and Ward

(4) BER VOLUME 2106.

(5) Morris, D. and J. C. McDonald, "Failure of Hyperimmune Gamma Globulin to Prevent Whooping Cough," Archives of Diseases of Children, 32:236-239, 1957.

(6) Place, E. H., et al., "Serotherapy in Pertussis," Journal of Pediatrics, 34:699-716, 1949.

GENERIC STATEMENT ON TETANUS ANTITOXINS

Tetanus is an acute disease of the nervous system caused by infection with the tetanus bacillus, Clostridium tetani, which produces an extremely potent neurotoxin that is lethal to man in miniscule amounts (approximately 7 millionths of a milligram). The tetanus bacillus also produces lesser reactive substances. The disease is of major importance, killing perhaps 1 million people worldwide annually. The tetanus bacillus is probably primarily a resident of the intestinal tract of various animals, but spores are widely distributed in soil and dirt, and when carried into devitalized injured human tissue that is low in oxygen, the spore form of the bacillus can germinate, liberate toxin and hence cause the disease. The disease can be prevented by immunization with tetanus toxoid. Immunization is indicated for everyone, since natural immunity, if it exists at all, is exceedingly rare in man; not even the disease itself produces immunity in those who recover from it.

In the 1890's, tetanus antitoxin was developed, primarily in horses, by hyperimmunization--first by injection of slowly increasing amounts of tetanus toxin, and later, when it became available, by sequential injections of tetanus toxoid. The serum from such animals contained varying amounts of antibody capable of neutralizing tetanus toxin in experimental animals; therefore it has been used on a worldwide basis ever since both for the prophylaxis of tetanus in unimmunized persons thought to be exposed to the disease, and for treatment of the disease.

Both the safety and efficacy of tetanus antitoxin of animal origin have been the subject of concern and disagreement ever since its introduction, because of the frequency of reactions--not infrequently severe and sometimes fatal--following the injection of horse serum in sensitive individuals, and because unequivocal data regarding its efficacy have never become available. Substitution of antiserum prepared in cattle or sheep did not solve either problem, and during the past 15 years attention has been turned to the preparation of concentrated antitetanus antibody solutions from immunized or hyperimmunized human donors. The human preparation, designated tetanus immune globulin, has eliminated the problem of reactions to heterologous serum, but the problem of efficacy remains unsettled. Nevertheless, the theoretical considerations and the clinical impression that either or both of these products are of value have led to their very general use, for prophylaxis of tetanus in previously unimmunized persons incurring a risk of contracting tetanus, and in the treatment of clinical tetanus.

Nature of Product

Tetanus antitoxin consists of the partially purified globulin fraction from the serum of animals (generally horses) hyperimmunized with multiple sequential doses of tetanus toxoid, and sometimes toxin as well. Potency in units is determined by reference to the U.S. standard antitoxin. Antitoxin of bovine or ovine origin is similar except for minor differences in the predominant type of antitoxin-containing globulin.

Tetanus immune globulin is the gamma globulin fraction from a pool of human donors who have either been selected because they already possess a sufficiently high serum antitoxin level against tetanus toxin, or else have been hyperimmunized so that their serum antitoxin level is suitably high.

Production

For the production of tetanus antitoxin, the best responders are selected from a number of horses that have been given several properly spaced injections of tetanus toxoid, and further immunized until test bleeding showed that their serum antitoxin level is high enough to yield a concentrated antitoxin of acceptably high titer, e.g., 1,500 units or more per ml. Present day harvesting of serum is done by plasmapheresis, collecting 8 to 9 liters of blood and retransfusing the separated cells, on a regular schedule such as every 2 weeks. The plasma is fractionated, usually by precipitation of the antitoxic antibodies with ammonium or sodium sulfate, yielding a mixture of proteins which contains a high proportion of the antitoxic globulin which is, in the horse, largely a beta-globulin. The precipitate is reconstituted, dialyzed and adjusted to yield approximately a 20 percent concentration of serum proteins. Further purification of the original serum is usually carried out under specified conditions of pepsin digestion, which hydrolyses much of the nonglobulin protein present, yielding a preparation with fewer nonspecific proteins and a higher ratio of beta-globulin, modified by digestion but still fully active against toxin. In practice, the proportion of specific antitoxin in the usual product is probably about 1 to 2 percent.

The digested, fractionated, dialysed product is adjusted to a concentration suitable for filling (either as prophylactic doses of 1,500 units or therapeutic doses commonly furnished as 10,000 units per vial). It is then tested for identity, safety and for potency in units per ml by mixture with toxin in graded dilutions and injection of each mixture into groups of guinea pigs. A preservative (usually thimerosal) is added, and the product is filled with a 20 percent excess or more, according to Federal regulations.

Tetanus immune globulin. Production from normal donors is based on availability of outdated blood from cooperating blood banks, and selection of those with high tetanus antitoxin titers, commonly selecting those which show 8 units or more by hemagglutination. Alternatively, selected hyperimmunized donors may be bled by plasmapheresis, yielding a human serum pool of higher titer than is obtainable from selected normal adult blood. In either case, the plasmas of at least 10 donors are pooled, and the pool is fractionated according to the alcohol method of Cohen et al., yielding a preparation with over 90 percent gammaglobulin and conforming to the limitations set by Federal regulations regarding the presence of other globulins. The immune globulin is stabilized with 0.3 M glycine, titrated for tetanus antitoxin content as with animal serums, and diluted before filling to contain approximately 16.5 percent globulin. A preservative (normally thimerosal 0.01 percent) is added. The usual preparation is distributed in 250 unit amounts (plus the standard excess required by regulations) in a volume normally ranging from 2 to 4 ml.

Use and Contraindications

Tetanus antitoxin, like tetanus immune globulin, may be used for the prevention of tetanus following tetanus-prone injuries in unimmunized individuals or those whose immunization status is uncertain, or for the treatment of clinical tetanus. For prophylaxis of injuries, tetanus antitoxin is generally considered to be indicated, if tetanus immune globulin is unavailable, in individuals having suffered injuries, burns, etc., judged by the physician as potentially at risk of developing tetanus. Prior to the injection of this material, the patient must be carefully questioned regarding any history suggesting sensitivity to horses or horse serum and should be tested for such sensitivity by conjunctival (1:10 dilution) or intradermal (1:100 dilution) test with the serum for freedom from reactions. Some experts advocate instead a "tolerance test" with 0.1 ml of a 1:100 dilution given subcutaneously. No test system is totally reliable and the patient must be watched for at least 1 hour after the antitoxin has been injected. The minimum dose is 1,500 units but most authorities agree that this is insufficient, and recommend a minimum of 3,000 units; some give 10,000 units routinely. If the wound is more than 24 hours old, some clinicians recommend doubling the dose. Epinephrine must be at hand at all times during testing and injection.

Special attention is required for babies born to unimmunized mothers under conditions conducive to neonatal tetanus. Such babies should be injected with 1,500 units of tetanus antitoxin or, if it is

available, 500 units of tetanus immune globulin (see below). Sometimes the mother is also at risk, in which case she should be given prophylaxis as outlined for any patient at risk of developing tetanus.

Tetanus antitoxin is contraindicated in individuals with a history of sensitivity to horses, horse dander or horse serum, and should be given with extreme caution to anyone who has previously received any injections containing horse serum. In the presence of clear-cut evidence of hypersensitivity, tetanus immune globulin should be used for prophylaxis even if its procurement means a delay of 24 hours. Although some believe that antibiotics are of value in the prophylaxis of tetanus, the available data do not support this belief. Nevertheless, antibiotics represent the only alternative when antitoxin-containing preparations are unavailable.

Prophylaxis with tetanus immune globulin is carried out without previous testing for sensitivity, but epinephrine should be at hand. The indications are the same as with antitoxin, but the dose is 1/3 to 1/6 the dose with equine antitoxin (250 to 500 units) since tetanus immune globulin is homologous and the half-life in vivo is about 3 weeks.

For therapy of tetanus, some clinicians prefer equine tetanus antitoxin because unlike tetanus immune globulin it can, with caution, be given intravenously and because 80 years of clinical experience has indicated that it may be of value. There is no general agreement as to the dose required for effective therapy, because it is quite evident that recovery from tetanus depends on many factors (sedation, debridement, prevention of spasms, prevention of infection, maintenance of

respiration, etc.). Theoretical considerations and certain studies support the view that little is gained by giving more than 5,000 to 10,000 units of antitoxin. Others advocate much larger doses. It is established that the only function of antitoxin is to neutralize freshly liberated toxin from the infected source, i.e., antitoxin does not neutralize toxin already fixed to tissues. It is customary to give 1/2 the selected dose intravenously, the other half intramuscularly, after following the test precautions outlined above for the use of the product in prophylaxis. An additional precaution is to give 0.1 ml intravenously and wait 1/2 hour. If this small dose is tolerated, the patient will generally tolerate the remainder, which should nevertheless be given extremely slowly since some patients react at higher thresholds than others.

There is no general agreement on the value of continued therapy with antitoxin after the initial dose. By 7 to 10 days after the first dose, the majority of patients are sensitized to the horse serum and rapidly eliminate the antiserum.

Therapy with tetanus immune globulin has now been practiced for about 15 years. With generally available preparations of tetanus immune globulin the product must be given intramuscularly (NOT intravenously) which delays absorption so that the peak titer of antitoxin in the patient's serum will not be reached for 2 to 3 days. However, some clinicians have found that tetanus immune globulin can be given very slowly by intravenous drip without untoward reactions. This practice

requires further study before endorsement. No firm guidelines regarding dosage exist, a commonly selected dose being 3,000 units. On the other hand, experimental animal studies suggest that the therapeutic dose of antitoxin is the same whether the serum is homologous or heterologous in origin; on this basis, at least 5,000 to 10,000 units of tetanus immune globulin should be given.

Preliminary sensitivity tests are not needed prior to injection of tetanus immune globulin; however, since patients will on rare occasions be sensitive to the preservative, to a specific allotype of globulin in the preparation, etc., therefore epinephrine should be at hand when this product is given.

Safety

Like other animal sera, equine tetanus antitoxin can cause serious or fatal anaphylactic reactions in a small proportion of people, and the discomfort of serum sickness in a much larger proportion of people. Therefore, its use always incurs at least a small risk. Parallel experience with prophylactic diphtheria antitoxin has disclosed about 1 death per 50,000 persons injected.

Being homologous in origin, tetanus immune globulin is almost reaction-free if given intramuscularly. However, it can cause alarming hypotensive reactions if given intravenously.

Efficacy

The use of tetanus antitoxin or tetanus immune globulin for the prophylaxis of tetanus is endorsed by most physicians on the basis of

logic and clinical experience, although unequivocal proof of efficacy is not available. Both preparations can protect animals under experimental conditions against either toxin or spore challenges. Data from World War I suggested, but did not prove, that antitoxin prophylaxis was of significant value. On the other hand, one reviewer has collected reports of 5,000 failures of tetanus antitoxin to prevent tetanus, and failures of prophylaxis have occured with tetanus immune globulin as well. Such data do not prove that the product is ineffective but they clearly show that there are limitations to its value. These may be due to inability to prevent fulminating tetanus, delay in prophylaxis, failure to prevent delayed tetanus, rapid metabolism of the antitoxin, and various other causes.

With regard to therapy, many reports have given conflicting results, but most reliable studies have tended to suggest that moderate doses of antitoxin are of some value, the optimal dose probably ranging between 10,000 and 20,000 units. However, as noted above, the role of antitoxin in the treatment of tetanus may be secondary to the crucial importance of sedation, maintenance of respiration and control of infection. Likewise, deaths from tetanus have occurred following the therapeutic use of tetanus immune globulin. Except for its freedom from the danger of reactions and from rapid elimination from the circulation of the host, tetanus immune globulin is subject to the same limitations as tetanus antitoxins: it cannot reverse the effects of toxin already fixed to tissue, and the clinical management of tetanus is the same

(except for serum reactions) with either agent. Clinicians will continue to use these products for treatment until they are fully evaluated despite incomplete evidence as to the efficacy of either agent for the treatment of tetanus.

The Panel believes that tetanus immune globulin and tetanus antitoxin (as an alternative) should be classifed as Category I for prophylactic purposes. Although unequivocal proof of effectiveness for this purpose is not available, theoretical considerations and uncontrolled clinical experience support an assessment of probable effectiveness. Furthermore, it is unrealistic to expect that a study could be defended that would withhold tetanus immune globulin (or tetanus antitoxin) from a patient for whom it would be indicated under the Public Health Services Advisory Committee on Immunization Practices guidelines on wound management.

On the other hand, the therapeutic use of tetanus immune globulin and/or tetanus antitoxin is a somewhat different matter for the reasons discussed above. There is far less of a consensus among clinicians concerning the therapeutic effectiveness of these products in cases of tetanus. The number of years required to obtain additional data are indeterminate and the possibility of controlled trials is very small because of the relatively low incidence of the disease and the probable low effect of the antitoxin. Although a Category IIIA was considered, the number of years required to obtain additional data are indeterminant and the possibility of controlled trials is very small. For this reason,

a Category I classification for therapeutic use of tetanus immune globulin and/or tetanus antitoxin is recommended.

Special Problems

In the United States, tetanus immune globulin has virtually superseded equine antitoxin for prophylactic use, but the equine product is still used in therapy, presumably because of its acceptability for intravenous administration and possibly because of cost and availability. Clearly, if the problem of intravenous use of tetanus immune globulin could be surmounted, there would be little reason for maintaining supplies of equine antitoxin. Furthermore, a number of preparations of tetanus immune globulin have been made experimentally, either in the United States or Europe, which appear suitable for intravenous use. Therefore, it appears that the problem of developing a satisfactory intravenous tetanus immune globulin product may be soluble.

Further evidence for the prophylactic and therapeutic efficacy of tetanus immune globulin is needed, but for ethical reasons a controlled study in the United States cannot be easily done. However, one comparison between tetanus immune globulin and equine antitoxin (in neonatal tetanus) has already been conducted, and no difference was noted. As indicated earlier, such a result is inconclusive as to the effectiveness of either agent inasmuch as untreated controls were not included.

Recently the old but discarded practice of intrathecal administration of equine antitoxin has been revived and is under systematic study overseas, using preparations free of the irritating preservatives which in the past apparently caused severe reactions. Such studies

should be watched with interest since they might have application to the similar use of appropriately modified tetanus immune globulin.

It should be noted that none of the above problems would exist if active immunization were universal.

Recommendations

1. Universal active immunization against tetanus should be promoted.

2. Support any studies necessary to establish the availability, safety, stability and potency of tetanus immune globulin suitable for intravenous use.

3. Support studies, clinical or in animals, to provide further information of value in judging the value of tetanus immune globulin in prophylaxis and therapy of tetanus.

4. Review and follow the accumulating data on intrathecal therapy with a view to its possible applicability to treatment of human tetanus with tetanus immune globulin.

5. Further information should be obtained regarding the possibility of a significant reduction in the reactivity of animal serum.

Basis for Classification

In the absence of controlled studies, difficult to obtain with this now rare (in the United States) life-threatening disease, the Panel could not insist on such evidence of efficacy. There is a sufficient body of historical data suggesting that tetanus antitoxin is of some effect, albeit marginal, in the treatment and prophylaxis of tetanus to justify classification in Category I.

BIBLIOGRAPHY

See Bibliography for tetanus toxoid.

SPECIFIC PRODUCT REVIEWS

TETANUS ANTITOXIN MANUFACTURED BY ISTITUTO SIEROTERAPICO VACCINOGENO TOSCANO SCLAVO

1. Description. This antitoxin is a sterile aqueous solution of enzyme-refined and concentrated immunoglobulins obtained from the plasma of horses hyperimmunized with tetanus toxin and/or toxoid. The plasma is pepsin-digested and precipitated in ammonium sulfate. The precipitate is collected, dialyzed, made up to 0.85 percent sodium chloride and 0.3 percent metacresol at pH 6.4, and filtered for bulk chilled storage. It is tested for titer, pyrogens, pH, electrophoretic composition, protein concentration, preservative concentration and sterility. These tests, plus tests for identity, potency, stability and total solids, are done for each filling which may be in vials holding 1,500, 3,000, 5,000 or 25,000 units (plus excess for dating as may be required).

2. Labeling--a. Recommended use/indications. This product is recommended for prevention and treatment of tetanus when tetanus immune globulin is not available. Prevention is indicated for individuals who have had 2 or less doses of tetanus toxoid and who have tetanus-prone injuries which are more than 24 hours old. Tetanus toxoid (plain or adsorbed) should be given in a different syringe at a different site, and the immunization completed later as per schedule.

Precautions include careful inquiries regarding allergies of any type and previous injections of serums. Skin tests (1:1,000, 0.1 ml intradermally) and eye tests (1 drop of 1:10 dilution into conjuctiva)

are mandatory. Normal saline controls should be used. Interpretation of skin test results is described. Epinephrine 1:1,000 should be at hand in a syringe. In the event of a positive sensitivity test, a so-called "desensitization" sequence of injections is described.

Adverse reactions of the various types included under "serum sickness" are said to occur in about 10 percent of patients, more frequently with larger doses. The usual dose is 1,500 to 5,000 units for prophylaxis, 50,000 to 100,000 for treatment.

b. Contraindications. Intravenous injections in patients showing positive sensitivity tests.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The submission to the Panel (Ref. 1) states that "The efficacy of the product has been confirmed by the good results obtained through the years in Italy and abroad" and cites 8 references including the American Academy of Pediatrics "Red Book" - but not Bianchi (Ref. 2) (who has collected reports of 5,000 prophylactic failures).

b. Safety--(1) Animal. Two thousand lots have been tested in guinea pigs and/or mice, with no unsatisfactory results. This product meets Federal requirements.

(2) Human. A few million vials have been marketed in the last 5 years without any "significant complaints" according to data submission.

c. Benefit/risk ratio. In the absence of tetanus immune globulin the available evidence indicates that the benefit-to-risk assessment for this product would be satisfactory for the recommended uses.

4. Critique. This is a standard enzyme-purified antitoxin which appears to be prepared and tested with all necessary precautions, and should be as safe and effective as any licensed tetanus antitoxins. The label does not explain the exclusion of this product from use in fresh wounds in the unimmunized.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS ANTITOXIN MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absense of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

TETANUS ANTITOXIN MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

No data have been provided by the manufacturer for tetanus antitoxin, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

TETANUS ANTITOXIN MANUFACTURED BY MERRRELL-NATIONAL LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

No data have been provided by the manufacturer for tetanus antitoxin, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

TETANUS ANTITOXIN MANUFACTURED BY PARKE DAVIS AND COMPANY

No data have been provided by the manufacturer for this product for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

TETANUS ANTITOXIN MANUFACTURED BY SWISS SERUM AND VACCINE INSTITUTE BERNE

No data have been provided by the manufacturer for tetanus antitoxin, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

REFERENCES

(1) BER VOLUME 2112.

(2) Bianchi, R., "Zur Serumprophylaxe des Tetanus," Helvetica Medica Acta, 29:2, 101-142, May 1962.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY ABBOTT LABORATORIES

1. Description. This is a 16.5 percent ± 1.5 percent solution of immunoglobulin prepared by cold alcohol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The product is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as a preservative. Plasma samples employed are nonreactive for hepatitis associated antigen.

2. Labeling--a. Recommended use/indications. This product is intended for passive immunization of patients with tetanus-prone injuries, especially when there is doubt of adequate immunity or if there is a history of severe reactions to tetanus toxoid. It is also indicated in the treatment of tetanus. It may be administered simultaneously with tetanus toxoid. The recommended prophylactic dose is 250 units; therapeutic dose data are not adequate although it is stated that doses ranging from 500 units in infants to 56,000 units in adults have been employed.

In general the labeling is rather vague and could be greatly improved by incorporating the Public Health Services Advisory Committee on Immunization Practices recommendations (or their equivalent) regarding wound management. The desirability of simultaneous active immunization with adsorbed toxoid should be stressed.

b. Contraindications. Avoid intravenous injection. Hypersensitivity reactions are rare, as with other immune globulins.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data relative to this manufacturer's product are given. Indeed it appears that Abbott Laboratories' has marketed this product only as a partially processed material (dry globulin powder) for further manufacture. There are apparently no data available. The manufacturer's submission to the Panel (Ref. 2) cites the general literature on the subject in support of efficacy.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No data relative to this product are given. Indeed no data are avilable even from marketing experience since the final product for which the license was granted has never been sold. Over a 5-year period, a few hundred Kg of the globulin power has been sold to other manufacturers.

c. Benefit/risk ratio. A benefit-to-risk assessment for this product cannot be determined.

4. Critique. Since there are actually no data at all on the safety and efficacy of the actual product for which a license was granted, and the licensed product per se has not been sold, there is no basis for any judgment. Theoretically, the product could be put through final processing and sold at any time, and there is no reason to think that it would be any less safe or effective than other marketed products.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for

administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY

ARMOUR PHARMACEUTICAL COMPANY

1. Description. Tetanus immune globulin (human) as manufactured by the Armour Pharmaceutical Company, is a sterile 10 percent to 18 percent solution of the immunoglobulin fraction prepared from plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic with glycine and contains up to 0.1 percent sodium chloride. The pH is adjusted with either sodium bicarbonate or acetic acid, and 0.01 percent thimerosal is added as preservative. It is packaged in 250 unit vials.

Human plasma is pooled and fractionated to freeze-dried Fraction II powder, using the alcohol fractionation method of Cohn. Fraction II is reconstituted in water, stabilizers and preservative are added, and the solution further processed to the final dosage forms. An extensive description of the process is made part of the submission.

2. Labeling--a. Recommended use/indications. This product is said to be indicated as a prophylactic agent in persons whose injuries are liable to tetanus infection. Although experience is limited, tetanus immune globulin (human) in large doses is stated as being possibly useful in the therapy of clinical tetanus.

b. Contraindications. None are specified. A precaution against intravenous administration is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The general body of data supporting the efficacy in humans of this product is cited in the submission to the Panel (Ref. 1), but no specific data relative to the Armour Pharmaceutical Company's product are provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data relative to the Armour Pharmaceutical Company's product are provided.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. The information supplied by the manufacturer, the animal tests that this product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human) is sufficient to place this product in Category I. The labeling should be more specific about indications for tetanus immune globulin prophylaxis in human. The recommendations of the Public Health Services Advisory Committee on Immunization Practices are quite specific on this point, and could well be reproduced in their entirety in the labeling. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY BUREAU OF LABORATORIES, MICHIGAN DEPARTMENT OF PUBLIC HEALTH

1. Description. This globulin is prepared from outdated blood or plasma donated to the Bureau of Laboratories, Michigan Department of Public Health from American Red Cross Regional Blood Centers, and Michigan Blood Banks affiliated with the Blood Salvage Program of the Michigan Department of Public Health. Outdated plasma containing significant amounts of tetanus antitoxin, as demonstrated by the hemagglutination test, is pooled and fractionated by the cold alcohol fractionation procedures of Cohn. The final product is prepared as a 15 to 18 percent protein solution to which 2.25 percent glycine has been added as a stabilizer, and 1:10,000 thimerosal is added as a preservative. It is distributed in 250 unit vials.

2. Labeling--a. Recommended use/indications. This product is intended for use in injured persons who need the immediate protection offered by tetanus antitoxin. Persons who have received the basic course of tetanus immunization are recommended to receive a booster dose of tetanus toxoid in preference to tetanus immune globulin. It is rather emphatically stated that the use of this material should be based on specific recommendations from full time health officers and/or the Division of Epidemiology of the Michigan Department of Public Health. For that reason the Public Health Services Advisory Committee on Immunization Practices recommendations are not reprinted as such.

A separate product, tetanus immune globulin (human) for therapeutic use, containing 2,000 units of tetanus antitoxin per bottle is also produced by this laboratory. The product under consideration therefore is for prophylactic use only, and contains 250 units of tetanus antitoxin, to be given intramuscularly.

b. Contraindications. None are listed. A precaution against intravenous administration is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data are provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data are provided. It is noted that thousands of doses of Michigan Department of Public Health's tetanus immune globulin have been distributed in Michigan since 1965, with no reports of adverse reactions having been received. There is no evidence that this particular product has been responsible for the transmission of hepatitis B virus.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product appears satisfactory.

4. Critique. This submission (Ref. 3) is brief, but generally complete and adequate. Information provided by the manufacturer, the animal tests the product is required to pass, together with the general body of data concerning tetanus immune globulin (human) are sufficient to determine this product to be safe and effective. The recommendations for use and indications should be clarified in the labeling. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY

CUTTER LABORATORIES, INC.

1. Description. Tetanus immune globulin (human), Hyper-Tet(R), is a solution of immunoglobulin prepared from venous blood of humans hyperimmunized with tetanus toxoid. Hyper-Tet contains 16.5 percent ± 1.5 percent protein dissovled in 0.3 M glycine and preserved with 1:10,000 thimerosal. The pH is adjusted with sodium carbonate.

Antibodies of homologous origin (as this product) have been shown to have a half life in the blood stream of 3.5 to 4.5 weeks.

Vials are said to contain 250 units of tetanus immune globulin, but the volume in which this is contained is not given.

The plasma is obtained exclusively by plasmapheresis (4 percent sodium citrate) and only donors of sufficient titers are selected.

Informed consent is obtained before a donor is enrolled in the program, and the donor's health appears to be adequately monitored by annual examination.

Only plasma from individual donors that is tested at each donation for hepatitis B antigen and is negative when tested by any one of the official Bureau of Biologics methods is used. Outdated preserved whole blood is used for fractionation into the components of plasma. According to the Bureau of Biologics directions, a minimum of 10 donors should be used. The Cohn cold alcohol fractionation method is utilized. No preservatives are added during the pooling of the plasma or fractionation.

The final product solution is sterilized by filtration. Sodium chloride U.S.P. is added to a final concentration of 0.45 percent.

2. Labeling--a. Recommended use/indications. This product is indicated in those patients who require immediate immunity against tetanus toxin, especially those who have little or no active immunity against it. It is also indicated in the regimen of treatment of active cases of tetanus.

In cases where the injury is severe and where the risk of potential tetanus infection is higher, a dose in excess of that recommended may be indicated. Dosage: for adults, 250 units should be given by deep intramuscular injection. In small children the dose may be calculated by the body weight (4.0 units per kg) or it may be advisable to administer the entire contents of the vial. The Public Health Service Advisory Committee on Immunization Practices is cited as a guide in wound management.

b. Contraindications. This product is contraindicated in individuals who are known to have had an allergic response to immunoglobulin.

It is warned that the product should not be given intravenously, since such injections, on occasion, cause a precipitous fall in blood pressure, and a picture not unlike anaphylaxis. Skin tests should not be carried out because the product is known to cause a localized area of inflammation which can be misinterpreted as a positive allergic reaction.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Several clinical studies consisting of measurement of antibody increase are reported in the submission to the Panel (Ref. 4) for this product. Twenty subjects were given 400 units of Hyper-Tet, and antibody levels compared with 15 subjects receiving 1,500 units of equine antitoxin. At first, serum levels were higher for those receiving the equine product in the high dosage, but after about 6 weeks higher levels of antitoxin remained among those receiving the human immunoglobulin.

Studies were also carried out measuring the response when subjects were given immunoglobulin alone or in combination with tetanus toxoid. Satisfactory (0.1) antitoxin levels were achieved with or without simultaneous administration of toxoid.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. References to safety reported in the literature are cited in the submission. The product is tested by several chemical tests as to content of protein, chloride, glycine, and for stability and pH, and electrophoretic identity.

c. Benefit/risk ratio. Although no human efficacy studies are available, on theoretical grounds the benefit-to-risk assessment should be satisfactory.

4. Critique. Labeling is satisfactory, although it may be desirable to give the approximate volume of plasma necessary to provide the

recommended dose of 250 units. No data from manufacturer's complaint files were provided. It is unclear how many donors are utilized for pooling of sera. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulaton that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY DOW CHEMICAL COMPANY

1. Description. Tetanus immune globulin (human), as produced by the Dow Chemical Company, is a sterile solution of immunoglobulin obtained from the pooled venous blood of humans hyperimmunized with tetanus toxoid. The contents of the vial or syringe are standardized to contain 250 units of tetanus antitoxin. It is prepared by cold alcohol fractionation stabilized with 2.25 percent glycine and preserved with 1:10,000 thimerosal. The plasma pools are fractionated by the Cohn cold alcohol fractionation method.

2. Labeling--a. Recommended use/indications. This product is said to be indicated for passive immunization of persons incurring wounds other than clean, minor wounds only when the history of tetanus toxoid administration is uncertain, or if only 1 or no toxoid injection has been administered; or if the wound has been unattended for more than 24 hours even with the history of 2 toxoid injections.

b. Contraindications. None are listed. A precaution against intravenous use is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The general body of literature supporting the efficacy of human tetanus immune globulin is cited in the submission (Ref. 5), but no specific data relative to the Dow Chemical Company's product are provided.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Ten human volunteers were given 250 units of tetanus immune globulin (human) intramuscularly, and observed immediately after

the injection, and once daily at 24, 48 and 72 hours. No unusual untoward reactions were noted in these 10 volunteers. The general body of data supporting the human safety of tetanus immune globulin (human) is cited as well.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. This submission is supported by a large number of reprints of data supporting the safety and efficacy of human tetanus immune globulin. Although little of the data applies directly to the Dow Chemical Company's product, the animal safety and efficacy tests, together with the general body of data supporting the safety and efficacy of human tetanus immune globulin is sufficient to place this product in Category I. See Generic Statement.

In the labeling, the recommendations for use should be clarified.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY E. R. SQUIBB & SONS, INC.

1. Description. This is a 16.5 percent solution of Cohn Fraction II obtained from plasma of selected donors immunized with tetanus toxoid. It is stabilized with 0.3 M glycine and contains 0.01 percent thimerosal as preservative.

2. Labeling--a. Recommended use/indications. This product is intended for passive immunization against tetanus. It is recommended for prophylactic use (250 units) in patients lacking a recent (5 year) history of active immunization or in those never immunized or of uncertain status. Therapeutic doses of 3,000 units or more (up to 6,000 units) are recommended as part of the treatment of clinical tetanus. The narrative of the package insert is fairly adequate, but would be improved from the user's point-of-view by including the Public Health Services Advisory Committee on Immunization Practices wound management recommendations in tabular form. Also, the advisability of adsorbed tetanus toxoid for simultaneous active immunization needs to be stressed.

b. Contraindications. Essentially none, except avoidance of intravenous injections. Hypersensitivity reactions are rare.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data on this product are given. The submission to the Panel (Ref. 6) refers to the American College of Surgeons 1972 recommendations and to a review by Heurich (Ref. 7) for prophylactic use of tetanus immune globulin and other aspects of management of tetanus.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data, not even the approximate number of doses distributed, are provided.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product can not be determined.

4. Critique. The manufacturer has supplied no information on human safety and efficacy for this specific product. The product does not appear to have been produced for a number of years.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked because this product has not been marketed for a number of years and there are insufficient data on labeling, safety, and effectiveness.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. This is a 10 to 18 percent solution of globulin derived from plasma of donors hyperimmunized with tetanus toxoid. The globulin is prepared by a modifed Cohn alcohol fractionation process and is dissolved in 0.3 M glycine containing not more than 0.25 percent sodium chloride. The preservative is thimerosal, 0.01 percent.

2. Labeling--a. Recommended use/indications. This product is intended for passive immunization against tetanus. For prophylactic use a dose of 250 units is recommended in injured individuals who have not been previously immunized with tetanus toxoid or for those with vague histories or with lapses of many years since the last booster. Prophylactic use is also recommended when the risk is great from extensive contaminated wounds. Simultaneous active immunization is also recommended. For treatment purposes in the management of clinical tetanus, it is noted that experience is limited and that doses of 3,000 to 6,000 units have been used with mixed results. The instructions given are rather vague and could be improved by incorporation of the Public Health Services Advisory Committee on Immunization Practices recommendations on wound management with appropriate updating of the literature references. They should also specify adsorbed toxoid for use in simultaneous active immunization.

b. Contraindications. Essentially those for immunoglobulin, especially avoiding intravenous injection. Hypersensitivity reactions are extremely rare.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Claims for efficacy are based on the identity of the product and are supported by a review in the submission (Ref. 8) of a number of literature citations relevant to the use of tetanus immune globulin in general. No specific data on this particular product are given.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No significant reactions were reported for 1970 to 1974. A few hundred thousand doses were distributed over a 5-year period. Some mild local inflammatory reactions for immunoglobulin given for measles were seen in 1.2 percent of cases in 1969. In general, immune globulin is a product of proven safety which rarely presents a serious problem. There is no serious question of safety for this product.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product is satisfactory.

4. Critique. There are no efficacy data in humans for this specific product. Tetanus immune globulin in a generic sense is an accepted product for the prophylaxis of tetanus where indicated. Its use along with other appropriate treatment is clearly accepted in cases of clinical tetanus although the appropriate dosage for this purpose is not clearly established. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

1. Description. This is a 16.5 percent (± 1.5 percent) solution of globulin prepared by cold ethanol fractionation of human plasma selected by hemagglutination tests to contain significant levels of tetanus antitoxin. It is stabilized by 0.3 M glycine and contains 0.01 percent thimerosal as a preservative.

2. Labeling--a. Recommended use/indications. This product is intended for passive immunization in persons at risk of tetanus who lack a reliable history of active immunization. It is stated that a booster response to tetanus toxoid (even after 20 years) is preferred to tetanus antitoxin. Doses of 250 units given intramuscularly are recommended for prophylaxis. Simultaneous active immunization with adsorbed toxoid is always recommended. No specific recommendations on therapeutic use are given; in this case the user is advised to contact the producer. In general, the labeling is brief and to the point, although it is less easy to follow than the Public Health Services Advisory Committee on Immunization Practices guidelines.

b. Contraindications. Essentially none. Avoid intravenous injection. Hypersensitivity reactions are rare.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Publications from the manufacturer's laboratory relative to the use of the product are cited in the submission (Ref. 9). These

pioneering and often cited papers document the recommended use of the 250 unit dose for prophylaxis as judged by maintenance of protective antitoxin levels. These studies document the feasibility and desirability of combined active-passive immunization, showing the superiority of adsorbed toxoid.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. From the years 1969 to 1973, thousands of 250 unit vials were distributed without incident. Considering the proven safety of immune globulin in general, there is no question of safety.

c. Benefit/risk ratio. The benefit-to-risk assessment for this product is satisfactory.

4. Critique. This is a brief, but well-documented report from a laboratory that helped pioneer the concept of tetanus immune globulin. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC.

1. Description. This product is a solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma drawn from donors who have been hyperimmunized with tetanus toxoid. The solution is dissolved in 0.3 molar glycine and contains thimerosal 1:10,000 added as preservative. The protein content is given as 10 to 18 percent globulin, and the antibody content is given as at least 250 units of tetanus antitoxin per dose.

The general procedure for immunization of donors is said to conform to the Federal regulations for source plasma, human.

2. Labeling--a. Recommended use/indications. This product is indicated in injured persons not actively immunized or in whom the immunization status is undetermined and who otherwise would be candidates for an injection of tetanus antitoxin for protection against the possibility of the development of tetanus. Passive protection need be considered only when the patient has had fewer than 2 previous injections of tetanus toxoid or when the wound has been untended for more than 24 hours.

The usual dosage for adults and children is 250 units (entire contents of one single-dose prefilled disposable syringe) regardless of body weight. The same dose is indicated for adults and children because theoretically the same amount of toxin will be produced in both.

More than 250 units may be indicated, together with antibiotics, when the risk of potential infection is great.

The advantages of using tetanus immune globulin rather than equine or bovine antitoxin are outlined. The product is also recommended for treatment of tetanus, but the dosage may vary, and it is said that 3,000 to 6,000 units have been used.

b. Contraindications. None are specifically given, but it is pointed out that the material should not be given intravenously, that local tenderness and stiffness of the muscles may occur after injection. Hypersensitivity to injections of immune serum globulin is mentioned as a possibility and in highly allergic individuals repeated injections may lead to anaphylactic shock or even death.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. Pertinent human studies are cited in the submission (Ref. 10) but no serologic studies of the manufacturer's product appear to have been carried out.

b. Safety--(1) Animal. This product meets Federal requirements.

(b) Human. No special testing of the manufacturer's product appears to have been carried out. However, between 1969 and 1974 a sizeable number of doses have been distributed without any reports of adverse reactions having been received.

c. Benefit risk/ratio. Assuming this product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. Critique. This is a rather brief application, which provides no specific data on the efficacy of the manufacturer's own product. The approximate volume containing 1 dose is not given. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY METABOLIC, INC.

No data have been provided by the manufacturer for tetanus immune globulin, for which they were licensed at the time this review was undertaken. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY OSTERREICHISCHES INSTITUT FUR HAEMODERIVATE G.M.B.H.

1. Description. This is a tetanus immune globulin of human origin containing, per ml, 250 United States units of tetanus antitoxin, 100 to 160 mg of total protein, 22.5 mg glycine, 3.0 mg sodium chloride, and 1:10,000 thimerosal as preservative. The product is said to be prepared from blood of healthy donors who had been immunized against tetanus. A good description of the production process is provided, which basically consists of passage of a plasma pool through an adsorption column, followed by cold ethanol fractionation. The final protein concentration varies between 10 percent and 16 percent w/v.

2. Labeling--a. Recommended use/indications. This product is said to be indicated in case of injury with risk of tetanus infection in instances in which adequate active immunity is not proven. "Adequate" active immunity is nowhere defined. Simultaneous active-passive vaccination is said to be indicated in cases of (1) lacking or inadequate active immunization or if definite history of immunization cannot be ascertained, (2) risk of antibody deficiency syndrome or reduced capacity of antibody formation, (3) risk of heavy contamination of the wound with tetanus bacilli, (4) injuries dating back longer than 3 days, and (5) serious burns.

b. Contraindications. The only contraindication listed is a previous severe reaction following the administration of tetanus immune globulin (human). A precaution against intravenous administration is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No data are provided. The submission (Ref. 11) contains an interesting report of 1 prophylactic failure in 1 case of a femur heavily injured by a slaughtering apparatus. The patient received active and passive immunization on the same day, but developed severe tetanus a few days later and died. The immunization history of this patient would have been of considerable interest.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. Radioimmunoassays for the determination of hepatitis B antigen are carried out on both the raw source plasma and the final product. The submission notes that no adverse reactions have been reported, and there have been no reports of transmission of hepatitis with this product. No prospective clinical data are presented, however.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product is satisfactory.

4. Critique. The information provided by the manufacturer, the animal tests which this product is required to pass, and the general body of knowledge concerning the safety and efficacy of human tetanus immune globulin are sufficient to place this product in Category I for prophylactic use.

No labeling was provided in the sense of a package insert. Pages 3 through 9 of the submission appear to serve the same purpose, and suffer significantly in the translation from German to English. Extensive revision will be necessary to put the language into contemporary usage.

"Adequate" active immunization must be defined, and reference should be made to official recommendations of advisory bodies such as the Public Health Services Advisory Committee on Immunization Practices. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY PARKE, DAVIS AND CO.

1. Description. This product is a concentrated solution of tetanus antitoxin as immunoglobulin prepared from the blood of adults who have been hyperimmunized with tetanus toxoid. It is prepared from plasma, which was nonreactive when tested for hepatitis B antigen. The globulin is precipitated by the Cohn cold ethanol fractionation process and supplied as a sterile standardized solution containing 100 to 180 mg of protein per ml (10 to 18 percent). The globulin fraction is dissolved in a 2.25 percent solution of aminoacetic acid (glycine), containing approximately 0.2 percent sodium chloride. It is preserved with 0.01 percent thimerosal and adjusted to approximately pH 6.8 with sodium acetate buffer.

2. Labeling--a. Recommended use/indications. This product is recommended for immediate passive immunization against tetanus as an emergency measure in persons sustaining other than clean minor wounds when immunization history is uncertain or when less than 2 doses of tetanus toxoid have been administered. When the wound is more than 24 hours old, however, the product should be given to patients who have received 2 doses of tetanus toxoid.

Tetanus immune globulin (human) is preferred over the similar product of equine or bovine origin.

The usual dosage for adults and children is 250 units regardless of body weight, although for children a dosage of 4 units per kg body weight may be adequate but larger doses are not harmful. The approximate

volume necessary to supply the recommended dosage is not given; the material is supplied in a syringe.

Larger doses (usually 3,000 to 6,000 units) of tetanus immune globulin (human) have been used therapeutically for treatment of clinical tetanus.

The use of combined active and passive immunization is discussed. If tetanus toxoid is not given immediately, active immunization with tetanus toxoid should be completed in all cases, either immediately or shortly after treatment.

b. Contraindications. None are stated, but it is mentioned under adverse reactions that reactions following intramuscular injections are infrequent and usually confined to the area of injection. Sensitization to repeated injections of tetanus immune globulin is said to be extremely unusual. As a precaution, the product should be administered intramuscularly, and not intravenously.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. The submission to the Panel (Ref. 12) includes referral to the pertinent literature only. This specific product appears not to have been evaluated in any form in humans.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No adverse experiences have been reported in a 5-year span between 1969 and 1974 from the use of hundreds of thousands of doses distributed worldwide. The company has received 61 complaints in

51 reports. The tetanus immune globulin was cloudy in 5 of these cases, the remaining reports related to packaging defects.

c. Benefit/risk ratio. Assuming the product is effective as discussed in the Generic Statement, the benefit-to-risk assessment should be satisfactory.

4. Critique. The selection and monitoring of donors is not described, neither is the method of obtaining informed consent described. Labeling is generally satisfactory, except that the approximate volume of the dose should be stated. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY TRAVENOL LABORATORIES, INC., HYLAND DIVISION

1. Description. Tetanus immune globulin (human), as produced by Travenol Laboratories, is a sterile 15 to 18 percent solution of immunoglobulin fraction of the plasma of persons who have been hyperimmunized with tetanus toxoid. The solution is made isotonic and stabilized with 0.3 molar glycine. It contains 0.1 percent sodium chloride and 0.01 percent thimerosal as a preservative. The globulin is precipitated by the alcohol fractionation technique of Cohn. It is packaged in 250 unit vials.

2. Labeling--a. Recommended use/indications. This product is said to be useful in the treatment of injured persons at risk of tetanus and who need the immediate protection offered by tetanus antitoxin. Since it is of human origin, it offers 2 advantages over an antitoxin of nonhuman (equine) origin: (1) the risk of immediate or delayed sensitivity reactions is practically nonexistent, (2) fewer antitoxin units are required to produce a longer lasting effect. The labeling is quite specific in terms of who should receive tetanus immune globulin, containing not only the specific recommendations of the Public Health Services Advisory Committee on Immunization Practices, but also a rather cogent discussion of the recommendations.

b. Contraindications. No absolute contraindications are listed. A precaution against intravenous administration is included.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data relative to the Travenol Laboratories' product are cited in the submission to the Panel (Ref. 13).

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No specific data relative to this product is cited.

c. Benefit/risk ratio. The benefit-to-risk assessment of this product appears to be satisfactory.

4. Critique. This submission, while brief, is quite to the point. Some specific details are provided relative to the testing for hepatitis B antigen, and to the hyperimmunization of donors. The information supplied by the manufacturer, the animal tests which the product is required to pass, and the general body of data regarding the safety and efficacy of tetanus immune globulin (human) as summarized in the Generic Statement on Tetanus Immune Globulin, are sufficient to place this product in Category I. For prophylactic use see Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

TETANUS IMMUNE GLOBULIN (HUMAN) MANUFACTURED BY WYETH LABORATORIES, INC.

1. Description. Tetanus immune globulin (human) is a sterile 16.5 (± 1.5) percent solution of human immunoglobulin prepared by Cohn cold ethanol fractionation of plasma from donors hyperimmunized with tetanus toxoid. The final product contains 0.3 molar glycine as a diluent and stabilizer and 0.01 percent thimerosal as a preservative. This product was prepared from blood that was nonreactive when tested for hepatitis B antigen.

Wyeth Laboratories purchases sterile tetanus immune globulin in bulk volume from Cutter Laboratories that has been released by the Bureau of Biologics. The product is used in the TUBEX hypodermic syringe. The manufacturing procedure for the Cutter Laboratories' product, for which there is a separate application, thus applies also to the Wyeth Laboratories' product, and the reader is referred to the product review for the Cutter Laboratories' product. In summary, the Cutter Laboratories' manufacturing process appears satisfactory.

The Wyeth Laboratories' product is designed to contain not less than 175 antitoxin units per ml. The degree to which this minimal potency level is exceeded is a direct function of the degree of hyperimmunization reflected in the donor plasma pool.

2. Labeling--a. Recommended use/indications. Tetanus immune globulin (human) is indicated for passive immunization against tetanus in any person with an injury that might be contaminated with tetanus

organisms, who has never been actively immunized with tetanus toxoid, or whose active immunity status is uncertain or of questionable validity and cannot be established. Passive immunization is probably also indicated for those persons actively immunized with tetanus toxoid whose last recall (booster) dose or last dose of the basic immunizing series (reinforcing dose) was given more than 10 years prior to injury and if a delay of more than 24 hours has occurred between the time of injury and initiation of specific tetanus prophylaxis.

The need to initiate active immunization with tetanus toxoid adsorbed at the same time as the human immunoglobulin is clearly spelled out.

The recommended adult dose is 250 units intramuscularly. The dose for children may be calculated on the basis of body weight (4.0 units per kg) or the entire contents of the TUBEX may be injected regardless of body weight since theoretically the same amount of toxin would be produced by infecting tetanus organisms regardless of whether the infection is occurring in an adult or child.

The half-life of tetanus immune globulin is approximately 4 weeks. In situations where the threat of tetanus persists or for treatment of the disease, repeated doses may be administered.

b. Contraindications. None is specifically mentioned, but local and systemic reactions are said to be infrequent and usually mild. The risk of isoimmunization is ever present when immunoglobulin is administered to immunologically competent persons. Under precautions, it is

warned that the product should not be given intravenously, since severe pyrogenic and fatal cardiovascular reactions have occurred following intravenous administrations. Tests for sensitivity should not be done.

3. Analysis. No specific analysis of efficacy or safety is outlined in this submission (Ref. 14). However, the product is purchased from Cutter Laboratories, for which a detailed separate submission is available. The reader is referred to the analysis of this product. Data on efficacy, based on studies of antitoxin in humans after administration of this product are available. No field trials have been carried out, neither would such an undertaking be feasible at the present time. No data from the complaint file are available.

a. Benefit/risk ratio. Since the product produces satisfactory levels of antitoxin in human subjects with originally low antitoxin levels, and the product appears to be safe, the benefit-to-risk assessment should be satisfactory.

4. Critique. The efficacy and safety of this product is the same as for the Cutter Laboratories' product. See Generic Statement.

5. Recommendations. The Panel recommends that this product be placed in Category I and that the license(s) be continued with the stipulation that labeling be revised in accord with the recommendations of this Report.

REFERENCES

(1) BER VOLUME 2108.

(2) BER VOLUME 2039.

(3) BER VOLUME 2071.

(4) BER VOLUME 2025.

(5) BER VOLUME 2087.

(6) "A Guide to Prophylaxis Against Tetanus in Wound Management," American College of Surgeons, 1972 Revision, pp 32-33, December 1972.

(7) Heurich, A. E., J. C. M. Brust and R. W. Richter, "Management of Urban Tetanus," Medical Clinics of North America, 57(6):1373-1381, 1973.

(8) BER VOLUME 2030.

(9) BER VOLUME 2055.

(10) BER VOLUME 2012.

(11) BER VOLUME 2115.

(12) BER VOLUME 2004.

(13) BER VOLUME 2107.

(14) BER VOLUME 2018.

MISCELLAENOUS PRODUCTS

COLLAGENASE MANUFACTURED BY ADVANCE BIOFACTURES CORPORATION, DISTRIBUTED BY KNOLL PHARMACEUTICAL CORPORATION

1. Description. Collagenase ABC ointment and collagenase santyl ointment contains the enzyme collagenase extracted from cultures of Clostridium histolyticum, suspended in a petrolatum base in a concentration of 250 units per gram. Collagenase is an enzyme which digests undenatured collagen fibers. Collagen is produced by fibroblasts and exists in the form of an interwoven fiber consisting of 3 strands which in turn are made up of a left handed poly-l-proline type helix. The ropelike coiled structure then has an apposite (right handed) supertwist. The uniqueness of collagenases compared with other proteolytic enzymes is that they attack the intact helical structure of collagen. Although collagenase from other sources are described, only that from Clostridium histolyticum has been produced in significant amounts for therapeutic application.

Other proteolytic enzymes employed in debridement act on fibrin and on denatured collagen but do not break up native collagen fibers which anchor the eschars of large ulcers, particularly burns, to the wound.

Collagenase is prepared from the supernatant of broth cultures of a standard strain of Clostridium histolyticum. The enzyme is concentrated by ammonium sulphate precipitation and the concentrate is sterilized by X-radiation. It is mixed with white petrolatum U.S.P. and

distributed in containers without preservatives. The potency of the enzyme is measured by an assay involving the digestion of bovine Achilles tendon and the subsequent measurement of liberated amino acids with ninhydrin reagent.

2. Labeling--a. Recommended use/indications. The ointment is recommended as a therapeutic debriding agent for dermal ulcers and burns and particularly to remove dense eschars which anchor necrotic tissue to the base of wounds and delay their epithelization. The enzyme is active at physiologic pH and temperature and loses activity rapidly at unfavorable conditions. The activity is also adversely affected by detergents, hexachlorophene and heavy metals such as mercury and silver which are contained in certain antiseptic solutions (e.g., Burow's Solution). Lesions must be thorougly washed with normal saline before applying collagenase. The ointment should be confined to the lesions and normal surrounding skin should be protected by dressings. Concurrent infection should be treated with topical antibiotics. Debilitated patients must be closely observed for the theoretical possibility of disseminated infection and bacteremia during the debridement. Crosshatching a thick eschar with a scalpel to increase penetration of the enzyme is helpful as is removing and loosening as much necrotic tissue as possible with forceps and scissors. Excess ointment should be removed with each daily change of dressing. It is appropriately pointed out that treatment of necrotic lesions other than dermal ulcers and severly burned areas have been limited only to reports of clinical observations without controls.

b. Contraindications. Since the enzyme is a protein, sensitization may develop with prolonged use although none has been reported. Adverse reactions have not been noted when used as recommended.

3. Analysis--a. Efficacy. Five controlled and 12 partially controlled studies are cited in the submission to the Panel (Ref. 1) as supporting evidence of efficacy. The 5 controlled studies were double-blind and included placebos. The controlled studies involved a total of 79 patients with dermal ulcers or decubiti. Some of these studies employed inactivated enzyme as placebo, were randomized and a relatively brief treatment period was evaluated to prevent obvious changes in the wounds from unblinding the study. Attempts were made to score the responses objectively by recording wound size, using serial photographs obtaining cultures and recording estimates of the amount and character of pus, debris, odor and inflammation. In all controlled studies there was a statistically significant difference in favor of collagenase over placebos in all measured parameters of wound healing (Table 1).

b. Safety. This product is well tolerated when used properly and no significant untoward effects have been reported except occasional erythema. Animal studies reveal a high level of tolerance and low toxicity in rabbits, mice and guinea pigs by injection of enzyme powder subcutaneously, intramuscularly and intravenously. Topical application in animals produces local erythema but no systemic toxicity. This product meets Federal requirements.

TABLE 1--SUMMARY TABLE-EFFICACY

Numier	Investigator	Exhibit Number[4]	Diagnosis	Patients Treated	Lesions Treated[1]	Satisfactory Response[2] E or G
1- Controlled Studies						
	Varma				C - 10	9
		34	Dermal ulcers; decubiti	20	P - 10	1
	German				C - 32	31
		13	Decubiti	34	P+- 22	5
	Bardfeld				C - 9	9
		2	Lower extremity ulcers	8	P+- 5	0
	Ambrus				C - 17	11
		1	Decubiti	10	P - 10	0
	Boxer		Venous or arterial ulcers;		C - 10	9
		7 & 8	decubiti	7	P - 7	1

[1] C = Collagenase, P = Placebo, P+ = Controls consisted of either placebo or other active agents.
[2] E = Excellent, G = Good.
[4] Refers to Exhibit in manufacturer's submission to the Panel (Ref. 1).

TABLE 1--SUMMARY TABLE-EFFICACY--con.

Number	Investigator	Exhibit Number[4]	Diagnosis	Patients Treated	Lesions Treated[1]	Satisfactory Response[2] E or G
2 - Partially controlled and uncontrolled studies						
	German				C - 15	12
		13	Decubiti	26	P - 11	1
	Boxer	7 & 8	P. V. ulcers and decubiti	40	C - 62	58
	Georgiev	12	Decubiti	21	C - 21	17
	Rein	31	Burns	6		6
	Barrett				C - 12	12
		3	Decubiti	12	P - 4	0
	Original submission				C - 327	270
		33	Dermal ulcers, burns	268	P+- 155	70

[1] C = Collagenase, P = Placebo, P+ = Controls consisted of either placebo or other active agents.

[2] E = Excellent, G = Good.

[4] Refers to Exhibit in manufacturer's submission to the Panel (Ref. 1).

TABLE 1--SUMMARY TABLE-EFFICACY--con.

Number	Investigator	Exhibit Number[4]	Diagnosis	Patients Treated	Lesions Treated[1]	Satisfactory Response[2] E or G
2 - Partially controlled and uncontrolled studies--con.						
	Lippmann	20	Dermal ulcers	40	C - 40	34
	Maxurek	24	Dermal ulcers, wounds; burns	1,356[3]	C - 1,356	1,085
	Zimmermann	37	Dermal ulcers	64	C - 64	Not reported
	Zimmermann	36	Burns	230	C - 230	Not reported
	Mahler	22	Extensive burns	59	C - 59	Not reported
	Blum	5	Dermal ulcers, decubiti; burns	71	C - 71	59
						Fair - Good

[1] C = Collagenase, P = Placebo, P+ = Controls consisted of either placebo or other active agents.
[2] E = Excellent, G = Good.
[3] Includes Zimmermann studies.
[4] Refers to Exhibit in manufacturer's submission to the Panel (Ref. 1).

c. Benefit/risk ratio. For use in the treatment of dermal ulcers and burns the ratio is satisfactory since the risk is small and with proper usage there is often significant improvement in the character of the wound without interference with antibiotic efficacy or other forms of treatment.

4. Critique. There is little question that this enzyme can digest intact collagen and that in large, eschared dermal ulcers described, such as those encountered in decubiti and burns, surface debridement can be enhanced, and that decrease in pus, inflammation and odor is quite regularly observed; adverse reactions are few. The labeling is accurate and pertinent and clearly defines the limitations of the product and instructions for its use. It is not clear, however, why in some labels, routine topical antibiotic treatment is insisted upon rather than advised when indicated by the degree of infection. Labeling for these products may have to be revised to discuss the possible interference of silver sulfadiazine or sulfamylon with the enzymatic activity of collagenase, an issue not fully resolved by the Fox, Stanford and Sampath paper (Ref. 2).

5. Recommendations. The Panel recommends that these products be placed in Category I and that the appropriate license(s) be continued because there is satisfactory evidence of safety and effectiveness for the products when used as recommended, provided the labeling is revised in accordance with this Report.

REFERENCES

(1) BER VOLUME 2119 and 2120.

(2) BER VOLUME 2118.

BIBLIOGRAPHY

(1) Bardfeld, L. A., "Treatment of Dermal Ulcers of the lower Extremity With Collagenase," In: Mandel, I. (editor), Collagenase, New York, Gordon and Beach, pp. 191-195, 1972.

(2) Boyer, A. M., N. Gottesman and H. Bernstein, "Debridement of Dermal Ulcers and Decubiti With Collagenase," In: Mandel, I. (editor), Collagenase, New York, Gordon and Breach, pp. 155-163, 1972.

(3) German, F. M., "Control of Dermal Ulcers With Collagenase," In: Mandel, I., (editor), New York, Gordon and Breach, pp. 165-169, 1972.

(4) Lee, L. K. and J. L. Ambrus, "Collagenase Therapy for Decubitus Ulcers," Geriatrics, 30(5): 91-93, 97-98, 1975.

(5) Varma, A. O., E. Bugatch and F. M. German, "Debridement of Dermal Ulcers With Collagenase," Surgery, Gynecology and Obstetrics, 136:281-282, 1973.

GENERIC STATEMENT

Streptokinase-Streptodornase

Streptokinase-Streptodornase is a mixture of extracellular enzyme activators and enzymes produced by some sero-groups of hemolytic streptococci. These agents liquify fibrin and nucleoproteins in purulent exudates. Streptokinase effects the conversion of plasminogen to plasmin, a proteolytic plasma enzyme. The latter digests fibrinogen and fibrin, resulting in fibrinolysis. Streptodornase is a group of enzymes which act in stages to liquify deoxyribonucleoprotein, the viscous cellular protein present in pus.

Tillett and Garner first described the fibrinolytic activity of hemolytic streptococci in 1933. By 1949 partial purification of the streptococcal extracellular enzymes that liquify pus was accomplished and the liquid preparation of Streptokinase-Streptodornase was introduced into therapy by Tillett and Sherry who instilled it into the pleural cavity to accomplish lysis of thick exudates. Topical use of the preparation for "enzymatic debridement" of purulent exudates was widely employed by 1950 and by 1955 intramuscular injections were tried for the nonspecific suppression of inflammation and edema in certain local infections. In 1958, buccal administration of tablets was introduced as an alternative to intramuscular injections and by 1960 clinical investigation of the effectiveness of oral tablets began, followed by marketing in 1963.

Production

The mixture of Streptokinase-Streptodornase employed in topical therapy is an extracellular product of a Group C strain of streptococcus grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins and a reducing substance. The culture filtrate is purified by the method of cold alcohol fractionation. A unit of streptokinase is the quantity required to produce from plasminogen an amount of plasmin sufficient to dissolve a standard fibrin clot in 10 minutes at 35° C. A unit of streptodornase is the quantity necessary to cause a decrease of 1 viscosity unit in 10 minutes at 30° C in a reaction mixture of 2.4 ml of deoxyribonucleic acid of a standard relative viscosity. The streptokinase-streptodornase mixture also includes a number of other streptococcal extracellular enzymes such as deoxyribonuclease, hyaluronidase, nucleotidase, and nucleosidase, all of which may contribute to the liquifying effect of the product on purulent exudates. The mixture is apparently free of streptolysin and proteinase. The solution is buffered with phosphate. Some preparations are mixed with carboxymethylcellulose 4.5 percent jelly. Mixtures are unstable at room temperature but retain full potency for 2 weeks when refrigerated at 2 to 10° C.

Labeling

1. Use and indications. Compatability with antibiotics is not yet clearly determined and it is recommended that antibiotics be administered separately. Streptokinase and streptodornase administered in solution either locally or parenterally are both antigenic and frequently elicit antienzyme antibodies. These antienzymes, antistreptokinase

and antistreptococcal DNAses may also appear after hemolytic streptococcal infections. A high titer is not harmful but requires increasing dosage of streptokinase-streptodornase to exert an effect. No antigenic responses have been reported for the buccal or oral forms but it is likely that they may also occur.

The rationale for topical or local administration of streptokinase-streptodornase is the augmentation of liquefaction of fibrin and pus where such action is considered desirable to produce healing more rapidly and to prevent extensive adhesions and fibrosis. The product does not act upon mucoproteins, fibroblasts, fibrous tissues or collagen in vivo although lysis in vitro has occasionally been reported.

Streptokinase is considered the most effective therapeutic agent available for enhancing the resolution of fibrin in closed body cavities containing inflammatory effusions (or clotted blood). It is superior to proteolytic enzymes for this purpose. Most inflammatory exudates contain plasminogen and the mechanism of fibrinolysis results from the diffusion of the plasminogen activator into the fibrinous substance resulting in production of plasmin within the fibrin network and thus rapid fibrinolysis. In addition, streptokinase is inactivated slowly (except by antistreptokinase) in contrast to proteolytic enzymes. On surface wounds, however, where proteolytic enzymes such as trypsin are not blocked by tissue inhibitors, plasmin is not as effective as other more widely active proteolytic enzymes. Thus, third degree burn eschars and necrotic connective tissues are not susceptible to plasmin digestion but are attacked by trypsin.

Except for the occasional presence of antistreptodornase, inflammatory exudates contain little which inhibits the activity of topically administered streptodornase. When streptodornase is administered systemically, however, its inactivation is rapid. For this reason parenterally administered streptokinase-streptodornase owes whatever specific effect it may have exclusively to streptokinase.

A peculiar situation exists, therefore, whereby streptokinase-streptodornase has been licensed for parenteral as well as topical use although any claim for parenteral efficacy would have to be unrelated to the action of streptodornase. Moreover, purified streptokinase for intravenous use in the treatment of thromboembolism is now available commercially and two preparations have recently been licensed.

The administration of streptokinase-streptodornase intramuscularly in dosages of 5,000 units of streptokinase twice daily has been recommended in the treatment of edema associated with infection and trauma, particularly cellulitis and thrombophlebitis, rather than extensive tissue necrosis. Claims have been made for rapid reduction in inflammatory reactions within a few days of initiation of treatment. About 10 percent of treated patients develop fever thought to be attributable to streptokinase-streptodornase. The recommended doses do not produce fibrinolysis, hematomas, petechiae or hemorrhage.

Package inserts recommend that streptokinase-streptodornase intramuscularly be accompanied by the systemic administration of a broad spectrum antibiotic agent. It is also emphasized that in the treatment of abscesses,

streptokinase-streptodornase, intramuscularly, may reduce accompanying cellulitis but should not replace sound surgical principles of drainage.

Administration (as recommended by current labeling). Streptokinase-streptodornase has been tried and recommended by the manufacturer for a long list of clinical applications. Appraisal of these are complicated and compounded by distinctions between topical application, local instillation into body cavities and abscesses, intramuscular administration, buccal tablets for parenteral administration and oral tablets.

Topical administration may be achieved in a variety of ways including dressing with streptokinase-streptodornase solutions, or application of streptokinase-streptodornase in a carboxymethlcellulose jelly. Instillation and irrigation in body cavities are effected by repeated applications and drainage as exudates are thinned.

Intramuscular streptokinase-streptodornase is recommended by the manufacturers for treatment of inflammation in inaccessible areas. It is suggested that such intramuscular injections deep into the gluteal muscle induce a "fibrinolytic response in areas of inflammation of any site." This is alleged to result in rapid reversal of the inflammatory process presumably by the digestion of fibrin in the edema fluid and reduction of the viscosity of the fluid.

Buccal tablets are recommended to produce results comparable to intramuscular administration. The tablets are placed in the buccal pouch or under the tongue and allowed to dissolve slowly for 10 minutes or more.

Oral administration is also advised on the grounds that gastric juice contains a considerable amount of "plasminogen proactivator" which reacts with streptokinase and the product is supposedly absorbed without inactivation.

Clinical applications suggested by manufacturers include: treatment of abscesses (by topical application only - parenteral has not been considered effective), bronchopulmonary inflammation by aerosol or instillation, or by systemic administration; cellulitis, ulceration and necrosis; gangrene from occlusive arterial disease (excluding dry gangrene); radiation necrosis; cervicitis; contusions, ecchymoses and hematomas (topical, intramuscular, and oral); cystitis, bladder clots, ureteral calculi (all forms of administration); dental and oral disorders, dermatological conditions (e.g., cystic acne vulgaris); empyema and hemothorax; nontuberculous purulent meningitis; suppurative joint infections; osteomyelitis; pericarditis; ophthalmic inflammation; puerperal pelvic conditions; pulmonary hyaline membrane syndrome; sinusitis and many other inflammatory conditions.

Thrombophlebitis and thromboembolic disease require special comment. Purified products of streptokinase are now licensed for intravenous and intraarterial therapy. Several cooperative trials have been conducted on the effectiveness of intravenous urokinase and streptokinase in pulmonary embolism and deep vein thrombosis and in myocardial infarction and other forms of arterial thrombosis. These and other studies have been summarized in several excellent recent reviews.

2. Contraindications and precautions recommended in current labeling--a. Topical and local use. Should be used only in areas where adequate drainage is maintained or in closed spaces, such as the pleural cavity when adequate drainage or operation is possible. A local increase of exudation and leukocytosis occurs in the first 24 hours. Pyrogenic reactions are the most common untoward effect. Allergic reactions are rare but the physician should be alert to the possibility of such reactions. Streptokinase-streptodornase is antigenic which limits the effectiveness of prolonged and repeated use.

b. Intramuscular use. Administration of broad spectrum antibiotics is advised concomitantly with the use of streptokinase-streptodornase intramuscularly. Appropriate surgical drainage is also urged. Defects in blood coagulation of liver disease are contraindications to parenteral use.

c. Buccal tablets are contraindicated in patients with reduced plasminogen or fibrinogen. Urticaria and rashes have been reported.

d. Oral tablets are also contraindicated in patients with reduced plasminogen and fibrinogen.

Safety

No reactions have been reported from 1969 through April of 1974 for the use of topical streptokinase-streptodornase produced by Lederle Laboratories.

Efficacy

To clarify considerations of safety and efficacy, the recommended uses of streptokinase-streptodornase should be clearly separated into three general categories: (i) debridement, (ii) anti-inflammation, and (iii) thrombolysis; and the effectiveness of each product should be considered in relation to these categories. (See Table 1.)

1. Debridement. On theoretical grounds, by in vitro studies, and by clinical observations, topical and local use of streptokinase-streptodornase can be expected to liquefy pus and blood clots in vivo in several conditions and under appropriate methods of application. Topical and local use of streptokinase-streptodornase may have efficacy in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be properly drained. Such uses are clearly only adjunctive to other medical and surgical procedures. The effectiveness of streptokinase-streptodornase can only be assessed, therefore, as a supportive rather than primary therapeutic agent. Furthermore, instruction for its usage must clearly define its major limitations as a topical agent - its substrates must be available and accessible and the enzymes and activators must be in continued contact with their substrates under physiological conditions of temperature and pH. For these reasons, instructions for the local and topical uses should be clearly subdivided into topographical categories, such as: (i) body cavities, (ii) wounds and fistulae, and (iii) the lumina of body passages (bronchi, urethra, external auditory canal, etc.).

Extensive lists of clinical conditions for which streptokinase-streptodornase is recommended by the manufacturer do not offer critical guidance to the selection of the appropriate clinical indications.

Body cavities. Streptokinase-streptodornase may be effective in liquefying pus and fibrin in certain body cavities as in the case of treatment of the appropriate stages of empyema or hemothorax, provided that adequate drainage is maintained. Lysis of inflammatory products and the local irritative effect of streptokinase-streptodornase cause an increased volume of fluid to accumulate in a closed cavity and the ease with which a cavity can be drained should be considered before employing the product. The use of streptokinase-streptodornase intrathecally is not generally recommended for primary forms of meningitis because of the severe local reactions it produces. The irrigation of neurosurgical drainage systems in certain cases of chronic obstruction of the cerebrospinal circulation may not be contraindicated, however, but would depend upon well informed clinical judgment as to its value. Instillation of streptokinase-streptodornase into body cavities probably offers the best opportunities to maintain local contact of the product with its substrates and yet it is not extensively employed in current practice because of other effective medical and surgical approaches to drainage of such cavities.

Wounds and fistulae. Topical therapy with streptokinase-streptodornase may also have adjunctive effectiveness in the treatment of

wounds and fistulae by enhancing debridement but the need for maintaining continuous contact with the surface of these lesions must be emphasized. Suspension of streptokinase-streptodornase in a jelly (such as carboxymethylcellulose) may facilitate such application, but again efficacy would depend upon the ingenuity with which wound contact is maintained with either solutions or pastes. There seem not to be significant reactions or contraindications to such topical use.

Luminal applications. The same issues, discussed above, apply to the efficacy of debridement of such tracts as the bronchi, urethra, auditory canals, etc. The clinical investigative evidence for the effectiveness of streptokinase-streptodornase in the debridement of these areas is even more difficult to assess than debridement of body cavities and wounds. So many variables are included in attempts to maintain good drainage of the respiratory, urinary and other tracts, that the design of an effective investigative protocol to demonstrate clear adjunctive efficacy of streptokinase-streptodornase would be very difficult if not impossible. Some degree of efficacy could be assumed, however, if the recommendations for topical use are followed closely.

2. Anti-inflammatory effects of streptokinase-streptodornase. The evidence of the parenteral use of streptokinase-streptodornase, either intramuscularly or by buccal tablets, or the use of oral tablets, is inadequate to establish these products as effective agents for reducing inflammatory reactions. The criteria of physiologic responses by which the systemic dose can be monitored are vague since the doses are below

the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent" response in complex multi-factorial diseases. Because streptodornase is inactive when given parenterally, the alleged anti-inflammatory effect should be due either to streptokinase activity or to the nonspecific effects of streptococcal proteins on host defenses. Because streptokinase activity by the dose and methods given cannot be demonstrated to be fibrinolytic, the remaining rationale for streptokinase-streptodornase as an anti-inflammatory agent might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of streptokinase-streptodornase as an anti-inflammatory agent.

3. Thrombolysis. In contrast to the intramuscular use of streptokinase-streptodornase, recent clinical investigation of highly purified and potent preparations of streptokinase and urokinase have been carried out in the treatment of thromboembolic diseases. Two purified streptokinase preparations have recently been licensed by FDA. An appraisal of clinical efficacy should be considered separately for each of the following indications:

a. Pulmonary embolism and deep vein thrombosis. It is difficult to separate these two indications because pulmonary embolism that does not arise from thrombi in the right heart is almost always associated with deep vein thrombosis. In pulmonary embolism the diagnostic tools

of angiography, ventilation - perfusion lung scans, and selective vascular catheterization have permitted quantification of the effects of thrombolytic agents on pulmonary emboli to an extent not possible with many other lesions. Although all recent studies were not always completely controlled, the universal observation has been more rapid resolution of the embolus than expected with conventional treatment and the parameters of improved functions measured were frequently statistically significant.

Similarly, it has been well demonstrated by venous angiograms in a statistically significant number of selected cases that thrombi in the deep veins of the lower extremity can be lysed and blood flow restored, at least temporarily.

In life-threatening pulmonary embolization, wherein obstruction of the pulmonary circulation is of a severe degree, intravenous streptokinase clearly improves blood flow. What is not yet proven by adequate clinical data is whether such use reduces mortality significantly, reduces subsequent embolization, or reduces damage to the lungs. Similarly, the demonstrated lysis of venous thrombi in the lower extremities does not yet establish that normal venous function has been restored, vascular damage avoided, pulmonary emboli reduced, or chronic venous insufficiency prevented. Further experience will be necessary to determine the degree of efficacy of intravenous streptokinase in this form of thromboembolic disease. Meanwhile, however, the Panel considers intravenous streptokinase with the licensed products to be effective to the extent described and within the limitations expressed.

b. Arterial thrombosis--(1) Myocardial infarction. Of 9 recent controlled clinical trials (Refs. 3 through 12), 3 early European trials showed a statistically significant decrease in mortality in patients treated with streptokinase for 18 to 24 hours as compared to controls. In general, trials in which only a minority of patients were studied in coronary care units suggested reduced mortality in patients treated with fibrinolytic agents; whereas 4 controlled randomized trials done entirely in coronary care units failed to verify these findings. Further trials are needed to clarify whether there are true benefits to be derived from treatment of myocardial infarctions with intravenous fibrinolytic agents.

(2) Peripheral arterial thrombosis. Although data for efficacy in acute arterial occlusion suggests some effect, especially in the more distal vessels of the lower extremity, the critical and urgent nature of such problems usually demand a surgical approach. Use of thrombolytic agents for peripheral arterial occlusion should probably be limited to clinically important lesions in patients who either are poor surgical candidates or in whom the indications for surgery are not absolute. Adequate data to establish efficacy are not yet available, however.

c. Retinal diseases. The reported experience of patient with retinal vascular disease treated with thrombolytic agents is generally anecdotal and insufficient to establish efficacy. Controlled studies with objective, double-blind measurements are, however, underway.

d. Complications of intravenous thrombolytic therapy. Fever appears to be a common reaction. A single dose of 100 mg of hydrocortisone intravenously have been administered routinely in several

investigative protocols presumably to reduce the febrile and "allergic" responses. No clear evidence for the value of corticosteroids administered this way is available. The nature of the pyrogenic reaction is also not clear. It may be hyperimmune or an endotoxin-like reaction to the streptococcal protein or it may be the result of rapid fibrinolysis. Skin testing in man to determine the local reactivity of the highly purified streptokinase products has not been done systematically.

Clearly allergic reactions (other than fever) have been remarkably few and have been more annoying than serious. A few cases have been reported wherein shock-like reactions resembling sublethal anaphylaxis have occurred. The nature of these are difficult to establish, but on theoretical grounds a rare truly anaphylactic reaction may be anticipated.

Bleeding is common from puncture sites, but serious hemorrhage occurs only occasionally and usually is due to underlying predisposing causes.

Antibodies to streptokinase are stimulated and they may increase refractoriness to repeated doses. More careful studies of these response and their possible relation to untoward reactions involving immune complexes should be made.

e. Contraindications of thrombolytic therapy. These are similar to contraindications of anticoagulant therapy; bleeding disorders, recent surgery, severe hypertension, gastrointestinal ulcers, diabetic retinopathy and recent cerebrovascular accidents.

Recommendations

For the sake of clarity, the accompanying table relates recommendations by major category of usage to the licensed products available.

1. Topical products. Category I is recommended for the topical use of streptokinase-streptodornase but only if the current labeling is revised to conform with the recommendations detailed above. The value of the suspension of the topical product in carboxymethylcellulose should be documented by further clinical evidence of effectiveness (Category IIIA).

2. The streptokinase-streptodornase products for intramuscular and oral use, including buccal tablets, have not been proved to be effective thrombolytic or anti-inflammatory agents. Category II is recommended for these.

3. The Panel considers the intravenous use of streptokinase with the licensed products to be effective to the extent described and within the limitations expressed. Further intensive investigation of streptokinase and urokinase in thromboembolic disease should be encouraged, bearing in mind that risk-benefit assessments will vary greatly in individual clinical conditions and circumstances.

Efforts to purify or synthesize urokinase should also be encouraged in order to substitute a naturally synthesized human product for a streptococcal protein.

TABLE 1--STREPTOKINASE-STREPTODORNASE

Indications	Topical		Tablets			
	Topical	Jelly	Intramuscular	Buccual	Oral	Intravenou
1. Debridement						
a. Body cavities	I (1)	--	--	--	--	--
b. Wounds and fistulae	I (1)	III A	--	--	--	--
c. Luminal	I (1)	--	--	--	--	--
2. Anti-inflammatory	--	--	II	II	II	--
3. Thrombolytic	--	--	II	II	II	I

I = Effective
II = Ineffective
IIIA = More clinical data required before efficacy can be determined.
-- = Not applicable
(1) = Revise labeling

BIBLIOGRAPHY

(1) Tillett, W. S. and R. L. Garner, "The Fibrinolytic Activity of Hemolytic Streptococci," Journal of Experimental Medicine, 58:485-502, 1933.

(2) Tillett, W. S. and S. Sherry, "The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent, and Sanguinous Pleural Exudations," Journal of Clinical Investigation, 28:173-190, 1949.

(3) Brogden, R. N., T. M. Speight and G. S. Avery, "Streptokinase: A Review of its Clinical Pharmacology, Mechanisms of Action and Therapeutic Uses," Drugs, 5:357-445, 1973.

(4) Frantantoni, J. C., P. Ness and T. L. Simon, "Thrombolytic Therapy. Current Status," New England Journal of Medicine, 293:1073-1078, 1975.

(5) Sasahara, A. A., W. R. Bell, T. L. Simon, J. M. Stengle and S. Sherry, "The Phase II Urakinase-Streptokinase Pulmonary Rmbolism Trial. A National Cooperative Study," Thrombosis et Diathesis Haemorrhagica, 33:464-476, 1975.

(6) Simon, T. L., J. H. Ware and J. M. Stengle, "Clinical Trials of Thrombolytic Agents in Myocardial Infarcation," Annals of Internal Medicine, 79:712-719, 1973.

VARIDASE, INTRAMUSCULAR MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. Each vial for intramuscular injection contains 20,000 units of streptokinase and at least 5,000 units of streptodornase with thimerosal 0.2 ml per vial added as a preservative. The production of streptokinase-streptodornase is as described in the Generic Statement. Two milliliters of sterile water for injection or sterile physiologic saline is added to the contents of a vial to make a solution containing 5,000 units of streptokinase per 0.5 ml for intramuscular injection. Procedures employed in the manufacturer of Varidase include standard tests for pyrogenicity in animals and sterility.

2. Labeling--a. Recommended use/indications. Intramuscular use of Varidase is recommended in the treatment of edema associated with infection and trauma. The best results are claimed in infections which do not produce necrosis of tissue such as thrombophlebitis, epididymitis and cellulitis. A beneficial effect on inflammation and edema with the use of this product is expected in all patients within 2 days after the start of treatment and in a small number of patients within a period of hours. An aggravation of the infection has not been observed in any of the patients but a rise in temperature attributable to streptokinase has been noted in about 10 percent of these patients. No significant change in prothrombin time nor in fibrinolysis can be detected at usual doses recommended. It is recommended that intramuscular use of Varidase

be accompanied by the administration systematically of a broad-spectrum antibiotic. The use of the product in patients with abscesses is not a substitute for sound surgical principles.

b. Contraindications. Varidase should never be administered intravenously. Varidase should not be injected intramuscularly when there is evidence of a defect in blood coagulation, or where liver function is depressed.

3. Analysis--a. Efficacy--(1) Animal. Not applicable.

(2) Human. Upon intramuscular injection, the mechanism by which streptokinase produces a reversal of the inflammatory process is not known. The streptodornase in the product is inactive when administered systemically. Parenteral administration has not been considered effective in the treatment of abscesses but is claimed to be effective in a wide variety of inflammatory lesions including bronchopulmonary inflammation (by either aerosol or systemic administration), gangrene from occlusive arterial disease, radiation necrosis, cervicitis, cystitis, pericarditis, osetomyelitis, etc.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No significant untoward reactions reported. Streptokinase and streptodornase are antigenic but allergic reactions are rare. The antibody response may require higher dosage to overcome inhibition of enzyme action but is not harmful.

c. Benefit/risk ratio. There is little risk in the use of the product but efficacy has not been demonstrated.

4. Critique. The criteria of physiologic responses by which the systemic dose of streptokinase can be monitored are vague since the doses are below the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent response" in complex multifactorial diseases and unmatched control series. Because streptodornase is inactive when given parenterally and streptokinase activity in the dose given cannot be demonstrated to be fibrinolytic or clearly antithrombotic, the only remaining rationale for streptokinase-streptodornase as anti-inflammatory therapy might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of streptokinase-streptodornase as an anti-inflammatory agent.

5. Recommendations. The Panel recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

VARIDASE, ORAL TABLETS MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. Each tablet contains 1,000 units of streptokinase and 2,500 units of streptodornase. Tablets are marketed as peach-colored, round, flat-faced, beveled tablets scored in half and 11/32 inches in diameter. The enzymes are prepared as described in the Generic Statement.

2. Labeling--a. Recommended use/indications. Varidase oral tablets are recommended for the same indications as the intramuscular preparation and for the reduction of edema and inflammation in the conditions mentioned in the Generic Statement. The average oral dose is 1 tablet (10,000 units of streptokinase) 4 times daily. In acute situations higher doses may be advisable. Normally treatment is continued for 4 to 6 days. Streptodornase is not believed to have therapeutic benefit in oral therapy.

b. Contraindications. Contraindicated in patients with reduced plasminogen or fibrinogen.

3. Analysis--a. Efficacy--(1) Animal. Not applicable.

(2) Human. Only streptokinase is involved in bringing about the desired clinical effect. The rationale for the use of tablets appears to be twofold: (i) Buccal absorption: Streptokinase is supposed to combine with salivary plasminogen and then to be absorbed by the buccal mucosa in quantities sufficient to convert plasminogen to plasmin. (ii) Intestinal absorption: Gastric juice contains considerable quantities of plasminogen which appears to be activated by streptokinase and

absorbed. Claims for clinical efficacy have been discussed in the Generic Statement on streptokinase-streptodornase.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. During the past 5 years there has been only 1 complaint of a reaction.

c. Benefit/risk ratio. There is little risk in the use of the product but benefit has not been demonstrated.

4. Critique. In addition to the lack of clear evidence that Varidase is absorbed from the gastrointestinal tract in a form which can produce the physiologic activity of streptokinase, the claims for significant clinical benefit from this route of clinical administration, as in the case of intramuscular therapy, are subjective and anecdotal and do not constitute adequate proof of efficacy.

5. Recommendations. The Panel recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

VARIDASE, TOPICAL MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. This product is a partially purified mixture of extracellular enzymes produced from a culture of Group C streptococci grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins and a reducing substance. The enzymatic actions on fibrin and pus are described in the Generic Statement. Each vial contains 100,000 units of streptokinase and 25,000 units of streptodornase and less than 100 units of streptolysin. The powder is dissolved in 10 to 20 ml of sterile water or normal saline. This dilution gives a solution containing approximately 5,000 to 10,000 units of streptokinase and 1,000 to 2,000 units of streptodornase per ml.

The identical product is available in a mixture with 4.5 percent carboxymethylcellulose jelly.

Procedures employed in the manufacture of topical Varidase include standard tests for pyrogenicity in animals and sterility.

2. Labeling--a. Recommenced use/indications. This preparation is recommended wherever clotted blood, fibrinous or purulent accumulations are undesirably present following trauma or infectious processes which have led to ulceration or abscess formation. The action of the enzymes results in the liquefaction of the 2 main viscous substances in inflammatory and purulent exudates, fibrin and nucleoprotein. A long list of suppurative conditions are suggested for topical treatment (see Generic State-

ment) on wounds or by instillation in body cavities such as the pleura, pericardium, bladder, sinuses, bronchi and joints.

b. Contraindications. Varidase should not be used in the presence of active hemorrhage and is not intended for and cannot act upon fibrous tissue, mucoproteins or collagens.

3. Analysis--a. Efficacy--(1) Animal. Not applicable.

(2) Human. May be effective for topical and local use in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be drained. Such uses are only adjunctive to other medical and surgical procedures. Its substrates must be available and accessible and the enzymes and activators must be in continued contact with their substrates under physiologic conditions of temperature and pH. Its use in body cavities, wounds and fistulae, and luminal areas should be effective only under conditions defined in the Generic Statement above.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No reactions have been reported from 1969 through April of 1974 for the use of topical streptokinase-streptodornase by Lederle Laboratories.

c. Benefit/risk ratio. Aside from the potential dangers of using this product in closed body cavities without adequate drainage, there is little risk in its topical use and the product is effective when its use is limited to well-defined situations.

VARIDASE WITH CARBOXYMETHYCELLULOSE JELLY TOPICAL MANUFACTURED BY LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.

1. Description. This product is identical to Varidase, topical, produced by Lederle Laboratories except for the addition of carboxymethylcellulose jelly, 4.5 percent. The mixture is then packaged in jars of jelly and vials of streptokinase-streptodornase with instructions to prepare a mixture by dissovling the contents of the vial in 5 milliliters of sterile water or normal saline and mixing this volume with the jar of jelly supplied.

2. Labeling--a. Recommended use/indications. The indications are the same as described for the use of Varidase, topical, when surface applications are made and when the use of the jelly will enhance maintenance of contact between the enzymes and the surface substrates. For application to the hands the jelly containing Varidase may be placed inside a loose rubber glove was fastened at the wrist.

b. Contraindications. No specific contraindications are noted for the addition of the jelly to topical varidase when used on surfaces as a debridement aid.

3. Analysis--a. Efficacy--(1) Animal. Not applicable.

(2) Human. May be effective for topical use in some situations where enhanced liquefaction of pus and fibrin is an aid to debridement and where the maintenance of contact between the enzymes and the substrates on the wounds may be enhanced by the use of a jelly.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) Human. No reactions have been reported through April of 1974 for the topical use of streptokinase-streptodornase.

c. Benefit/risk ratio. There is no apparent risk to the topical use of this product and the issue of efficacy is limited to its use in well-defined situations and to the method of maintaining the product in contact to the surface to which it is applied.

4. Critique. The topical use of this product may be of some use in the specific situations defined in the Generic Statement when the addition of jelly to the mixture will assist in maintaining enzyme-substrate contact. No clear clinical evidence has been presented, however, that specifically pertains to the advantages of the addition of the jelly to topical solutions of Varidase.

5. Recommendations. The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed three years, during which time the manufacturer shall provide evidence for the effectivness of this product, provided that the labeling is revised in accordance with the recommendations in this Report.